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| <p>(51) International Patent Classification ⁷ : C07K 14/47, G01N 33/68, A61K 38/08, 38/10, C07K 7/06, 7/08</p> | | A3 | <p>(11) International Publication Number: WO 00/05254 (43) International Publication Date: 3 February 2000 (03.02.00)</p> |
| <p>(21) International Application Number: PCT/EP99/05050 (22) International Filing Date: 16 July 1999 (16.07.99)</p> | | <p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> | |
| <p>(30) Priority Data: 98202470.5 23 July 1998 (23.07.98) EP</p> | | <p>Published <i>With international search report.</i></p> | |
| <p>(71) Applicant (for all designated States except US): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).</p> | | <p>(88) Date of publication of the international search report: 15 June 2000 (15.06.00)</p> | |
| <p>(72) Inventors; and (75) Inventors/Applicants (for US only): VERHEIJDEN, Gijsbertus, Franciscus, Maria [NL/NL]; Heischouw 7, NL-5345 XT Oss (NL). BOOTS, Anna, Maria, Helena [NL/NL]; Ver- lengde Torenstraat 10, NL-5366 AV Megen (NL).</p> | | | |
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(54) Title: NOVEL PEPTIDES FOR USE IN IMMUNOTHERAPY OF AUTOIMMUNE DISEASES

(57) Abstract

The invention relates to the use of novel peptides in a peptide induced tolerance therapy to prevent autoimmune disorders and in particular their use in treatment of chronic destruction of articular cartilage. The invention furthermore embraces pharmaceutical compositions comprising said peptides and a diagnostic method for the detection of autoreactive T cells in a test sample.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/05050

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | | |
|-------|-----------|-----------|-----------|-----------|----------|
| IPC 7 | C07K14/47 | G01N33/68 | A61K38/08 | A61K38/10 | C07K7/06 |
| | | | C07K7/08 | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | <p>WO 98 06859 A (HUMAN GENOME SCIENCES INC ; THOTAKURA NAGESWARA RAO (US); CHOPRA AR) 19 February 1998 (1998-02-19) Residues 334-342 of hpmfw51 figure 3</p> <p>---</p> | |
| A | <p>EP 0 805 206 A (SMITHKLINE BEECHAM CORP) 5 November 1997 (1997-11-05) residues 306-314 of seq ID 2. page 3, last paragraph</p> <p>---</p> | |
| A | <p>WO 96 13517 A (AKZO NOBEL NV ;BOOTS ANNA MARIA HELENA (NL); VERHEIJDEN GIJSBERTUS) 9 May 1996 (1996-05-09) abstract</p> <p>---</p> <p>-/-</p> | |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

*** Special categories of cited documents :**

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

Date of mailing of the international search report

21 March 2000

28/03/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/05050

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | WO 97 40068 A (AKZO NOBEL NV ;BOOTS ANNA MARIA HELENA (NL); VERHEIJDEN GIJSBERTUS) 30 October 1997 (1997-10-30) seq id 41 ----- | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/05050

| Patent document cited in search report | Publication date | Patent family member(s) | | | Publication date |
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| | | ZA 9703071 | A | 05-08-1998 | |

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION
(PCT Rule 61.2)

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| Date of mailing (day/month/year) 05 April 2000 (05.04.00) | in its capacity as elected Office |
| International application No. PCT/EP99/05050 | Applicant's or agent's file reference O/98393 WO |
| International filing date (day/month/year) 16 July 1999 (16.07.99) | Priority date (day/month/year) 23 July 1998 (23.07.98) |
| Applicant VERHEIJDEN, Gijsbertus, Franciscus, Maria et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

14 February 2000 (14.02.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

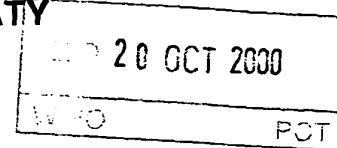
was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference O/98393 WO | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/EP99/05050 | International filing date (day/month/year) 16/07/1999 | Priority date (day/month/year) 23/07/1998 |
| International Patent Classification (IPC) or national classification and IPC C07K14/47 | | |
| Applicant AKZO NOBEL N.V. et al. | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application | | |

| | |
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| Date of submission of the demand 14/02/2000 | Date of completion of this report 18.10.2000 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Valcarcel, R Telephone No. +49 89 2399 2368 |



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05050

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

Description, pages:

1-15 as originally filed

Claims, No.:

1-8 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:

the claims. Nos.:

the drawings sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 702(c)).

4. Additional observations, if necessary:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/05050

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|----------------------------|
| Novelty (N) | Yes: | Claims 1-8 |
| | No: | Claims NONE |
| Inventive step (IS) | Yes: | Claims 1-8 (ALL PARTIALLY) |
| | No: | Claims 1-8 (ALL PARTIALLY) |
| Industrial applicability (IA) | Yes: | Claims 1-8 |
| | No: | Claims NONE |

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/EP99/05050

Re Item I

The sequence listing was also taken into account for examination.

Re Item V

1. The present application **does not satisfy the criterion set forth in Article 5 PCT because the subject-matter of claims 1 to 8 is not sufficiently disclosed.**

According to Article 5 PCT the description shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art.

Examples 1 to 5 of the present application relate to the peptide HSFTLASAETTVG, corresponding to the amino acids 266-278 of the YKL-39 protein (SEQ ID NO:2). Example 1 discloses the homologous sequences in proteins YKL-39 and macrophage chitotriosidase (Chi) to the peptide corresponding to the amino acids 263 to 275 of the HC gp-39, which was known to induce the most prominent immune response as an autoantigen in patients with rheumatoid arthritis (RA), see page 4 of the description of the present application, first paragraph. The homologous sequences are peptides YKL-39 (266-278) and Chi (269-282).

Example 2 discloses that the YKL-39 (266-278) peptide, which does not accommodate the effective DRB1*0401 peptide binding motif, binds with high affinity to DR4 (B1*0401).

In example 3 it is further disclosed that the YKL-39 (266-278) peptide is able to generate an immune response similar to HC gp-39 (263-275), and example 4 discloses that the YKL-39 (266-278) peptide is recognized in RA patients. Furthermore, the YKL-39 (266-278) peptide was shown to induce tolerance to a peptide-specific response induced with HC gp-39 (263-275), see example 5.

Claim 1 refers to a peptide having an amino acid sequence of 9-55 amino acid residues comprising the amino acid sequence FTLASAETT (SEQ ID NO:1).

Nowhere in the description there is an indication that any other peptides that HC gp-39 (263-275) and YKL-39 (266-278) would have the effect of causing tolerance to a peptide-specific response induced with HC gp-39 (263-275),

which appears to be an essential feature of the invention.

In particular, examples 2 and 3 of the present application disclose that although the peptide Chi (269-282) is able to bind with high affinity to DRB1*0401, it does not generate an immune response similar to HC gp-39 (263-275).

Although the peptides referred to in claim 1 have 9 amino acid residues identical to that of YKL-39 (266-278), this does not imply that they have the same effects as the YKL-39 (266-278) peptide. The only peptide falling under the scope of claim 1 which has been shown to perform the essential features of the invention is the **YKL-39 (266-278)** peptide.

Thus, the subject-matter of claim 1 is not sufficiently disclosed and as a consequence, this claim and all the claims referring to it (claims 2 to 8) **do not satisfy the criterion set forth in Article 5 PCT.**

2. If the peptides, other than the YKL-39 (266-278) peptide, referred to in claims 1 to 8 do not have the effect disclosed for the YKL-39 (266-278) peptide, then they do not solve the technical problem, which can be regarded as to provide alternative peptides which have the effects of HC gp-39 (263-275).

Compounds which do not solve a technical problem cannot be regarded as being inventive and therefore, these compounds do not satisfy the criterion set forth in Article 33(3) PCT. Therefore, the subject-matter **of claims 1 to 8 does not involve an inventive step.**

3. Only if **all the peptides** under the scope of claims 1 to 8 (as the peptide FTLASAETT, or a peptide comprising the sequence HSFTLASAETTVG and additional amino acids) **have the effects disclosed for the YKL-39 (266-278) peptide**, then claims 1 to 8 could be considered inventive. At present the IPEA only acknowledges novelty, inventive step and industrial applicability of the particular YKL-39 (266-278) peptide (SEQ ID NO:2).